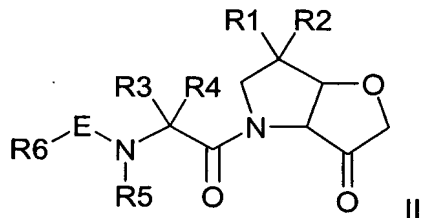


Claims

A compound of the formula II



wherein

one of R¹ and R² is halo and the other is H or halo;

R³ is C₁-C₅ straight or branched chain, optionally fluorinated, alkyl;

R⁴ is H; or

10 R³ together with R⁴ defines

a spiro-C₅-C₇ cycloalkyl, optionally substituted with 1 to 3 substituents selected from halo, hydroxyl, C₁-C₄ alkyl or C₁-C₄ haloalkyl; or optionally bridged with a methylene group; or

a C₄-C₆ saturated heterocycle having a hetero atom selected from

15 O, NR_a, S, S(=O)₂;

R⁵ is independently selected from H or methyl;

E is -C(=O)-, -S(=O)_m-, -NR⁵S(=O)_m-, -NR⁵C(=O)-, -OC(=O)-,

R⁶ is a stable, optionally substituted, monocyclic or bicyclic, carbocycle or heterocycle wherein the or each ring has 4, 5 or 6 ring atoms and 0 to 3 hetero atoms selected from S, O and N and wherein the optional substituents comprise 1 to 3 members selected from R₇;

20 R₇ is independently selected from halo, oxo, nitrile, nitro, C₁-C₄ alkyl, -XNR_aR_b, -XNR_bR⁹, -NR_bC₁-C₄alkylR⁹, NH₂CO-, X-R⁹, X-O-R⁹, O-X-R⁹, X-C(=O)R⁹, X-(C=O)NR_aR⁹, X-NR_bC(=O)R⁹, X-NHSO_mR⁹, X-S(=O)_mR⁹, X-C(=O)OR⁹, X-NR_bC(=O)OR⁹;

25 R₉ is independently H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, phenyl, any of which is optionally substituted with R¹⁰;

R_{10} is independently selected from hydroxy, XR^9 , $-XNRaRb$, $-XNRbR^9$, $-NRbC_1-C_4alkylR^9$, nitro, cyano, carboxy, oxo, C_1-C_4 alkyl, C_1-C_4 -alkoxy, C_1-C_4 alkanoyl, carbamoyl;

X is independently a bond or C_1-C_4 alkyl;

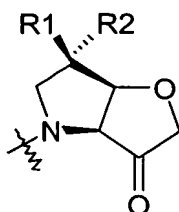
5 Ra is independently H, C_1-C_4 alkyl or $CH_3C(=O)$;

Rb is independently H, or C_1-C_4 alkyl

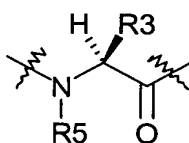
m is independently 0, 1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

10 2. A compound according to claim 1, wherein the stereochemistry is as depicted in the partial structure below:



15 3. A compound according to claim 1, wherein the stereochemistry is as depicted in the partial structure below:



4. A compound according to claim 1, wherein R^2 is halo and R^1 is H.

5. A compound according to claim 4, wherein R^2 is fluoro.

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6. A compound according to claim 1, wherein R^1 and R^2 are fluoro.

7. A compound according to claim 1, wherein R^3 is C_1-C_4 branched chain alkyl.

25 8. A compound according to claim 7, wherein R^3 is iso-butyl.

9. A compound according to claim 1, wherein R^3 and R^4 together define spirocycloalkyl.
10. A compound according to claim 9, wherein R^3 and R^4 together define spirocyclohexyl.
11. A compound according to claim 1, wherein R^5 is H.
12. A compound according to claim 1, wherein E is $-C(=O)-$.
13. A compound according to claim 1, wherein R^6 is substituted phenyl.
14. A compound according to claim 13, wherein the substituent comprises $-NRaRb$, $-CH_2NRaRb$, $-NRbR^9$, $-NRbC_1-C_4alkylR^9$, C_1-C_4 straight or branched alkyl or $-O-R^9$.
15. A compound according to claim 14, wherein the substituent comprises $-NH-CH_2phenyl$, $-NHCH_2pyridyl$ or $-NH-phenyl$, wherein each phenyl or pyridyl ring is substituted with $C_1-C_4-alkyl$, $-NRaRb$, $-NRbR^9$ or $-NRbC_1-C_4alkylR^9$.
16. A compound according to claim 13, wherein the substituent comprises C_3-C_6 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, phenyl, any of which is optionally substituted with R^{10} .
17. A compound according to claim 16, wherein the substituent is selected from indolinyl, pyranyl, thiopyranyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, any of which is optionally substituted with R^{10} .
18. A compound according to claim 17, wherein the substituent is thiazolyl, 5-methylthiazolyl or thienyl, optionally substituted with R^{10} .
19. A compound according to claim 18, wherein the substituent is thiazol-4-yl, 5-methylthiazol-4-yl or thien-2-yl, optionally substituted with R^{10} .

20. A compound according to claim 18, wherein the thiazolyl, 5-methylthiazolyl or theinyl is substituted with morpholinyl, morpholinylmethyl-, piperidinyl, piperidinylmethyl-, piperazinyl, piperazinylmethyl, any of which is substituted with C₁-C₃ alkyl, fluoro, difluoro or C₁-C₃ alkyl-O-C₁-C₃alkyl-.
21. A compound according to claim 20, wherein the substituent to the thiazolyl, 5-methylthiazolyl or thienyl is piperid-4-yl which is substituted with methyl, piperazinyl which is N-substituted with C₁-C₃ alkyl or methoxyethyl-, -or piperid-1-ylmethyl- which is unsubstituted or 4-substituted with fluoro or di-fluoro.
22. A compound according to claim 13, wherein the substituent comprises a morpholine, piperidine or piperazine ring, optionally substituted with R¹⁰.
23. A compound according to claim 22 comprising piperid-4-yl or N-piperazinyl, N-substituted with Ra or piperidin-1-yl which is 4-substituted with -NRaRb.
24. A compound according to claim 1, wherein R⁶ is optionally substituted: benzothiazol or benzofuryl or benzoxazolyl.
25. A compound according to claim 24, wherein the substituent is -OR⁹, -OXR⁹, -NRbR⁹ or -NRbXR⁹.
26. A compound according to claim 25, wherein R⁹ is piperid-4-yl, piperazin-1-yl or piperidin-1-yl or morpholino, any of which is substituted with C₁-C₃ alkyl.
27. A compound according to claim 26, wherein the optional substituent to R⁶ is N-morpholinylethyloxy, N-methylpiperid-4-yloxy, or N-methylmorpholin-3-ylmethyloxy.
28. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 27 and a pharmaceutically acceptable carrier or diluent therefor.

29 Use of a compound as defined in any of claims 1-27 in the manufacture of a medicament for the treatment of disorders mediated by cathepsin K.

30 Use according to claim 29, wherein the disorder is selected from:

- 5 osteoporosis,
 gingival diseases such as gingivitis and periodontitis,
 Paget's disease,
 hypercalcaemia of malignancy
 metabolic bone disease
- 10 diseases characterised by excessive cartilage or matrix degradation, such as
 osteoarthritis and rheumatoid arthritis.
 bone cancers including neoplasia,
 pain.

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